(X)
all cls.

(12) UK Patent Application (19) GB (11) 2 307 857 (13) A

(43) Date of A Publication 11.06.1997

(21) Application No 9524758.1

(22) Date of Filing 04.12.1995

(71) Applicant(s)
Euro-Celtique S.A

(Incorporated in Luxembourg)

122 Boulevard de la Petrusse, Luxembourg

(72) Inventor(s)
Stewart Thomas Leslie
Sandra Therese Antoinette Malkowska
Derek Allan Prater
Trevor John Knott
Hassan Mohammad

(74) Agent and/or Address for Service
Marks & Clerk
57-60 Lincoln's Inn Fields, LONDON, WC2A 3LS,
United Kingdom

(51) INT CL^6
A61K 9/46 31/135

(52) UK CL (Edition O)
A5B BLM B180 B43Y B431 B48Y B482 B58Y B586 B59Y B596 B64Y B640 B831

(56) Documents Cited
EP 0361680 A1

(58) Field of Search
UK CL (Edition O) A5B BHA BJA BJB BLM
INT CL^6 A61K 9/46 31/00
ONLINE: CAS ONLINE; DIALINDEX/MEDICINE, PHARM, WPI

(54) AN EFFERVESCENT TABLET CONTAINING TRAMADOL

(57) An effervescent pharmaceutical formulation contains tramadol, or pharmaceutically acceptable salt thereof, and an acid base couple which preferably comprises citric acid or tartaric acid and sodium hydrogen carbonate, sodium carbonate or sodium biphosphinate.

GB 2 307 857

AN EFFERVESCENT FORMULATION

CASE NO: P/0430

The present invention relates to effervescent formulations in particular an effervescent pharmaceutical formulation and especially such a formulation containing tramadol or a pharmaceutically acceptable salt thereof as a pharmaceutically active ingredient.

Effervescent formulations are widely known and are generally solid preparations containing an acid/base couple which, when the formulation is brought into contact with water, reacts with the production of carbon dioxide and consequent bubbles and effervescence. The effervescence feature leads to rapid disintegration of the dosage form and thus the rapid and complete dissolution of the active ingredient(s).

Effervescent formulations containing aspirin include PLATET® (Nicholas UK) which is indicated for the prevention of graft occlusion following coronary bypass surgery and ALKA-SELTZER® effervescent tablets (Bayer UK) which is indicated for headache with upset stomach. This latter preparation is known to function as antacid by neutralising gastric acid.

From EP-A 492247 is known an effervescent formulation containing an H_2-blocker which is suitable for self-medication by consumers for the relief of upset stomach associated with heartburn, sour stomach or acid indigestion.

EP-A 369228 and EP-A 228164 describe effervescent tablets containing ibuprofen as the active ingredient. Ibuprofen is a medicament with an analgesic and anti-inflammatory activity similar to that of aspirin.

British Patent No. 1328591 and EP-A 203768 both disclose soluble acetaminophen effervescent compositions, and effervescent compositions containing acetaminophen are marketed for the treatment of mild to moderate pain or as antipyretics.

WO 93/13760 describes effervescent preparations containing e.g. loperamid (an antidiarrhoeal) or diclofenac (an anti-inflammatory).

Tramadol is a strong opioid analogue analgesic which was disclosed in British patent No. 997399 in 1965. The only preparations containing tramadol or a pharmaceutically acceptable salt thereof so far marketed are in the form of normal release capsules, drops, injections and controlled release matrix tablets in which the tramadol or salt is combined with neutral excipients.

There has been no suggestion or teaching in the art, that tramadol or salt thereof could usefully be presented in an effervescent formulation.

According to the present invention there is provided an effervescent formulation comprising tramadol or a pharmaceutically acceptable salt thereof in association with an acid/base couple.

The preparations may be in any solid physical form used in the pharmaceutical field, and will preferably be a powder, beads, pellets or granules, or tablet which may be obtained by compressing the powder, beads, pellets or granules.

The preparation, in addition to the acid/base couple and active ingredient, may contain a binder, which may be a conventional binder material used in known effervescent preparations such as compressible sugars or polyvinyl pyrrolidone.

In one embodiment the preparation comprises tramadol and an acid/base couple dispersed in a matrix comprising a thermosoftening binder which is preferably a fusible material which melts or softens below 150°C: preferably such a thermosoftening binder is a hydrophilic water soluble substance such as a polyethylene glycol (PEG) of molecular weight 1000 to 20000, preferably 1000 to 6000.

Also, the preparation may additionally contain the usual excipients e.g. diluents, sweeteners and flavourings.

The acid/base couple may be present in an amount corresponding to 10% to 90% by weight of the formulation.

The acid/base couple may be a conventional acid/base couple, comprising an organic acid e.g. citric acid or tartaric acid and an inorganic base e.g. sodium hydrogen carbonate, sodium carbonate or sodium biphosphinate.

Preferably the acid is citric acid. A preferred acid/base couple contains citric acid and sodium hydrogen carbonate and sodium carbonate.

It is well known that tramadol has an extremely bitter taste. The preparation marketed as drops contains saccharose, cyclamates and flavourings, and a known controlled release tablet formulation has been film coated to mask the bitter taste. We have surprisingly found that a formulation containing tramadol or pharmaceutically acceptable salt thereof and an acid/base couple, when dissolved in an appropriate amount of water, is of surprisingly acceptable palatability with an unexpectedly low degree of bitterness even in the absence of sweeteners.

The preparation in accordance with the present invention can be prepared by any suitable, conventional method. For instance powdered tramadol or salt thereof and the components of the acid base couple may be simply dry mixed and compressed to form tablets.

Preparations in accordance with the invention may also be prepared by granulating a mixture of the tramadol or salt thereof with a granulating agent and admixing the components of an acid/base couple in particulate form with the granules. The granules and particles of the acid/base couple may be suitably size screened and if necessary, the granules may be sized by grinding or screening.

Preparations in accordance with the invention may also be prepared by e.g. wet granulating a mixture of tramadol or salt thereof, an acid and, if desired, other components e.g. saccharin sodium, followed by drying and mixing with the base of the acid/base couple. The resulting granular mixture may then, if desired be compressed into tablets.

One preferred process for the production of an effervescent preparation comprises mechanically working in a mixer/granulator e.g. a high shear mixer, such as a Collett Gral 10 or equivalent mixer, a mixture of the dry components of an acid/base couple in particulate form, the tramadol or salt thereof in particulate form, and a particulate binder which melts or softens at a temperature of from 35°C to 150°C and optionally an organic, water soluble release enhancing material, at a speed and energy input which allows the binder to melt or soften whereby it forms agglomerates or granules. The various components may be incorporated with the mixture at various stages. In one embodiment a mixture is formed by mechanically working the base, any optional components and the binder and the acid added subsequently. Alternatively the acid may be incorporated into the mixture before the base. The incorporation of the acid and base at different time points in the mechanical working serves to maintain their separation and reduces the risk of any premature reaction. We have found that it is advantageous to remove all or substantially all free moisture from at least some of the ingredients such as the base of the acid/base couple and any of the optional ingredients, such as the release enhancing component, and the tramadol or salt thereof before mechanical working commences. This may advantageously be carried out by warming these components to e.g. 60-70°C under reduced pressure. The agglomerates or granules may be further processed, after cooling, to provide unit dosage forms. In a preferred embodiment the agglomerates or granules are broken down to give particles e.g. by passing through a suitably sized screen of a Jackson Crockatt or equivalent milling machine or by extruding to form rods which may be cut into tablets or by moulding into tablets, or extrusion through a multiplicity of small diameter holes e.g. 0.5-1.0mm and cutting of the extrudates with a blade to form pieces e.g. 0.5-1.5mm. The further processing may comprise filling into sachets or compressing the particles or extruded pieces to form tablets in known manner. The tramadol or salt thereof can be incorporated into the mixture of the binder and acid/base couple preferably before or shortly after commencement of the mechanical working.

EXAMPLE 1

Tablets were manufactured each containing the following ingredients:-

	mg
Tramadol HCl D.A.C.	50.0
Citric acid anhydrous Ph. Eur.	990.0
Saccharin sodium Ph. Eur.	5.0
Sodium hydrogen carbonate Ph. Eur.	1,162.0
Sodium carbonate anhydrous B.P.C.	81.0

The ingredients were directly mixed in a suitable blender, discharged and compressed on a tablet press.

EXAMPLE 2

Example 1 was repeated but using the same materials in proportion to produce tablets having the following ingredients:-

	mg
Tramadol HCl	50.0
Citric acid anhydrous Ph. Eur.	495.0
Saccharin sodium Ph. Eur.	2.5
Sodium hydrogen carbonate Ph. Eur.	581.0
Sodium carbonate anhydrous B.P.C.	40.5

EXAMPLE 3

Tablets were manufactured containing the following ingredients:-

	mg
Tramadol HCl	50.0
Citric acid anhydrous Ph. Eur.	495.0
Polyethylene glycol 6000 Ph. Eur.	100.0
Saccharin sodium Ph. Eur.	2.5
Sodium hydrogen carbonate Ph. Eur.	581.0
Sodium carbonate anhydrous B.P.C.	40.5

The ingredients were blended in a mixer/granulator equipped with heating facility (heated jacket and/or microwave heater). The temperature was increased to about 60°C whilst mixing until granulation occured. Then the mixture was cooled and if necessary classified by passing through a suitable screen/mill. The resulting granules were compressed into tablets.

EXAMPLE 4

Tablets were manufactured containing the following ingredients:-

Tramadol base	44.0
Citric acid anhydrous Ph. Eur.	495.0
Saccharin sodium Ph. Eur.	2.5
Sodium hydrogen carbonate Ph. Eur.	581.0
Sodium carbonate anhydrous B.P.C.	40.5

The ingredients were blended in a mixer/granulator equipped with heating facility (heated jacket and/or microwave heater). The temperature was increased whilst mixing until granulation occured. The granules were cooled and if necessary classified by passing through a suitable screen/mill. The resulting granules were compressed into tablets.

EXAMPLE 5

Tablets similar to those described in Examples 1 to 4 were prepared but without saccharin sodium Ph. Eur.

REFERENCE EXAMPLE 6

Tablets according to the preceding Examples were added to a volume of water and dissolved rapidly i.e. within 2 to 3 minutes with effervescence. The tastes of the resulting solutions were found to be palatable with a low degree of bitterness.

CLAIMS

1. A solid effervescent pharmaceutical preparation comprising a pharmacologically effective amount of tramadol or a pharmaceutically acceptable salt thereof in association with an acid/base couple.

2. A preparation according to claim 1, in the form of a tablet, or powder, pellets or granules in unit dosage form.

3. A preparation according to claim 1 or 2, wherein the acid of the acid/base couple is citric acid.

4. A preparation according to any one of the preceding claims, wherein the acid/base couple is present in an amount of 10% to 90% by weight.

5. A preparation according to any one of the preceding claims wherein the active ingredient is tramadol hydrochloride.